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Adherence to antidepressant medications is associated with reduced premature mortality in patients with cancer: A nationwide cohort study

Gal Shoval. M.D.[1,2,3], Ran D. Balicer, M.D., Ph.D., M.H.A.[1,6], Becca Feldman, Ph.D.[1], Moshe Hoshen, Ph.D.[1], Gilad Eger, M.D.[2,3], Abraham Weizman, M.D.[2,3,5], Gil Zalsman, M.D., M.H.A,[2,3,4,5], Brendon Stubbs, Ph.D.[7], Pavel Golubchik, M.D.[2,3], Barak Gordon, M.D., M.H.A.[8,9], Amir Krivoy. M.D.[1,2,3,7]

1 Clalit Research Institute, Chief Physician Office, Clalit Health Services, Tel Aviv, Israel

2 Geha Mental Health Center, Petah Tiqva, Israel

3 Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Aviv, Israel

4 Felsenstein Medical Research Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

5 Division of Molecular Imaging and Neuropathology, Department of Psychiatry, Columbia University, New York, NY, USA.

6 Public Health Department, Faculty of Health Sciences, Ben-Gurion University, Beer-Sheva, Israel

7 Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London Box SE5 8AF, United Kingdom and South London and Maudsley NHS Foundation Trust, Denmark Hill, London, United Kingdom

8 Medical Corps, Israeli Defense Forces

9 Faculty of Medicine, Hebrew University, Jerusalem

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Corresponding Author:

Prof. Gal Shoval, MD

Director, Child and Adolescent Division

Geha Mental Health Center

P.O. Box 102, Petah Tiqva 49 100, Israel

Telephone: 972-3-925-8440, Fax: 972-3-925-8276; E-Mail: shovgal@tau.ac.il

ABSTRACT

Background: Depression and anxiety are common in cancer and antidepressants (AD) are an efficacious treatment. The relationship between AD adherence and mortality in cancer is unclear. This study aimed to evaluate the association between adherence to AD and all-cause mortality in a population-based cohort of patients with cancer.

Methods: We conducted a four-year historical prospective cohort study including 42,075 patients with cancer who purchased AD at least once during the study period. Adherence to AD was modeled as non-adherence (<20%), poor (20%-50%), moderate (50% - 80%), and good (>80%) adherence. We conducted multivariable survival analyses adjusted for demographic and clinical variables that may affect mortality.

Results: During 1,051,489 person years at risk follow-up, the adjusted hazard ratios (HR) for mortality were 0.89 [95%CI: 0.83–0.95], 0.77 [95%CI: 0.66-0.72] and 0.80 [95%CI: 0.76–0.85] for the poor, moderate and good adherence groups, respectively, compared to the non-adherent group. Analysis of the entire sample and a subgroup with depression, for cancer subtypes revealed similar patterns for breast, colon, lung and prostate cancers, but not for melanoma patients. Multivariate predictors of premature mortality included male gender (HR 1.48 [95%CI: 1.42–1.55]), current/past smoking status (HR 1.1, [95%CI: 1.04-1.15], p <0.0001), low socioeconomic status (HR 1.1, [95%CI: 1.03-1.17], p<0.0001) and more physical comorbidities.

Conclusions: The present study is the first to demonstrate that higher adherence to AD is associated with a decrease of all-cause mortality in a large nationwide cohort of cancer patients. Our data add to the pressing need to encourage adherence to AD among cancer patients.

Key words: antidepressants; mortality; cancer

INTRODUCTION

Prevalence rates of major depression among cancer patients are four times higher than the general population (Bortolato et al., 2017; Ostuzzi, Matcham, Dauchy, Barbui, & Hotopf, 2015) and up to a quarter of oncologic patients have clinically significant depressive and anxiety symptoms (Mitchell et al., 2011; Pirl, 2004). These rates increase in patients with poorer prognosis (Benton, Staab, & Evans, 2007) and in end stages of the disease (Lo et al., 2010). Depression in cancer patients has been associated not only with a substantially reduced quality of life (Grassi et al., 1996), greater physical distress (Chen & Chang, 2004) and prolonged hospital stays (Prieto et al., 2002), but also with poorer adherence to the cytotoxic medications (Colleoni, Mandala, Peruzzotti, Robertson, Bredart, & Goldhirsch, 2000), that in turn may aggravate the chance for survival. Most notably, co-morbid depression in patients with cancer was compellingly established as an independent risk factor for suicide (Chochinov, Wilson, Enns, & Lander, 1998) as well as rapid cancer progression and mortality (Lloyd-Williams, Shiels, Taylor, & Dennis, 2009; Pinquart & Duberstein, 2010; Satin, Linden, & Phillips, 2009). A recent large population-based study in England indicated a 2-4 fold elevated risk of suicide in patients with certain cancers and that suicide risk was highest in the first 6 months following cancer diagnosis (Henson, Brock, Charnock, Wickramasinghe, Will, & Pitman, 2018).

To-date, only scarce and methodologically-limited reports yielding contradictory data are available on this issue (Ostuzzi et al.,2015; Ostuzzi, Matcham, Dauchy, Barbui, & Hotopf, 2018). There have been three recent systematic reviews of pharmacologic treatment for depression in patients with cancer (Ng, Boks, Zainal, & de Wit, 2011; Rodin, Lloyd, Katz, Green, Mackay, & Wong, 2007; Williams & Dale, 2006), which

provided mixed evidence for the effectiveness of antidepressant drugs (AD) for depression and none evaluated their effect on mortality. In a cohort of 17,883 patients with either colorectal cancer or glioma, there was no significant mortality reduction in those who used tricyclic antidepressants (TCA) (Walker, Grainge, Bates, & Card, 2012). A similar finding was found in a study examining the use vs. non-use of any AD in a sample of 1,306 women with breast cancer (Chubak, Buist, Boudreau, Rossing, Lumley, & Weiss, 2008). In contrast, in another cohort of 3,058 breast cancer patients, there was a 50% increased risk of all-cause mortality in those who used AD (Wernli, Hampton, Trentham-Dietz, & Newcomb, 2011). Moreover, a randomized controlled trial of sertraline vs. placebo was suspended after the pre-planned interim analysis of the first 189 participants indicated that patients who received sertraline had a significantly shorter survival time than the placebo group (adjusted hazard ratio 1.62) (Stockler et al., 2007).

Depression and anxiety are treatable in medically-ill patients (Ramasubbu et al., 2012), but there is still a lack of a pharmacological treatment algorithm for the use of AD in patients with cancer (Okamura et al., 2008; Reich, 2008). This task may be challenging not only due to the dearth of consistent knowledge regarding the effect of AD on the mortality of these patients, but also because present analyses have not taken into account the actual adherence of the patients to AD.

Whereas AD are widely prescribed internationally (Beck et al., 2005; Kivimaki et al., 2007), low adherence is commonly reported among AD users, with or without cancer. A recent case-control study comparing AD adherence among 1142 women with breast cancer and pre-existing depression and 1142 matched non-cancer patients with pre-existing depression revealed similar adherence (70%) for both groups (Chou, Winn,

Rosenstein, & Dusetzina, 2017). Wider-scale pharmacoepidemiological studies showed similar rates of adherence in non-cancer patients with depression and anxiety. In a report of an antidepressant compliance program including 13,128 patients, rates of partial or full non-adherence were 75%, dropping later to 40% of days without dispensed AD being used (Bambauer et al., 2006).

Patient adherence rates to AD reflect the actual longitudinal consumption of AD, and are measured as a continuous variable, rather than dichotomous use or non-use which is far less informative. Previous nationwide cohort studies have found a beneficial effect of good adherence to AD for reducing premature mortality in the general population (Krivoy et al., 2016), cardiovascular patients (Krivoy et al., 2015), Parkinson Disease (Shoval et al., 2017) and stroke patients (Krivoy et al., 2017). To the best of our knowledge, no previous study has investigated the association between AD adherence and mortality in people with cancer. Given this pertinent gap, we conducted a nationwide cohort study to investigate whether higher AD adherence was associated with lower mortality in the patient population with cancer. Our secondary objective was to evaluate mortality among different types of cancer as function of AD adherence.

METHODS

We used the nationwide database of Clalit Health Services (CHS), described in detail previously(Krivoy et al.,2016). Briefly, this computerized database utilizes data from the integrated medical records of the largest health provider in Israel, which covers over 4 million patients across the lifespan, equating to approximately 53% of the population. Health provision in Israel is mandatory for each resident and service users have incentive to use the public services due to subsides and low cost of medical services.

Population and study period

We retrospectively analyzed the entire CHS patient population during the study period (1.1.2008-1.1.2012) at all ages (N=4,056,700). We included all patients with at least one prescription for an AD during the study period and a clinical diagnosis of Malignant Neoplasms – ICD 10 code C (N=55,306). All Food and Drug Administration (FDA) approved AD were included based on the WHO Anatomical Therapeutic Chemical (ATC) code N06A. In the final analyses we included only AD users, namely patients who purchased at least one prescription (N=42,075). Access to the data warehouse and the analyses were approved for this study by the CHS Review Board.

Measures

Outcome

A record of all-cause mortality was the primary outcome during the four-year study period, captured from linked data produced by the Ministry for Interior Affairs. Patients were followed-up from the entry to the study (i.e. prescription of AD) until death or the end of the study period.

Main predictor

Adherence to antidepressants

The adherence measure was modeled on the basis of the concept of medication possession ratio (data from CHS-owned pharmacies) with the addition of physician prescription data (derived from EMR) in accordance with previous research (Krivoy et al., 2015; Krivoy et al., 2016; Krivoy et al., 2017; Shoval et al., 2017; Singer et al., 2012). Only less than 3% of CHS patients get their prescriptions filled in a non-CHS owned pharmacies. Study participation duration was calculated as the continuous period between the first and the last prescribed AD. Adherence was defined as the period of AD **purchased** prescriptions (months), during follow-up, divided by study participation duration (months). Thus it reflects adherence over the period for which AD were known to be prescribed (and therefore indicated). Adherence (medication possession ratio) was calculated across all AD used. Switching between different AD compounds was not taken into account, and was considered as continuous use of AD.

$$Adherence\ (\%) = \frac{\text{Duration of } \mathbf{purchased} \text{ AD prescriptions (Months)}}{\text{Duration of continous } \mathbf{prescribed} \text{ AD (Months)}} X\ 100$$

Adherence is reported as a percentage score for each patient. Similarly to previous literature (Krivoy et al., 2015; Krivoy et al., 2016; Krivoy et al., 2017; Shoval et al.,2017), patients with adherence below 20% were considered non-adherent, those with 20%-50% adherence were considered poorly adherent, those with 50%-80% were considered to have a moderate adherence and patients with adherence above 80% were considered to have good adherence. In accordance with previous research, we did not model adherence as a continuous variable, since our previous study demonstrated no superiority when considering adherence as a continuous versus the categorical variables described here (Krivoy et al., 2016).

Covariates

We collected the following socio-demographic and clinical variables at study entry: age (categorized into 0-18, 18-24, 24-40, 40-64, 65-74, 75-84, 85+ years), gender, socioeconomic status and self-reported smoking status (categorized as those who never smoked and those who smoked in the past or present). We extracted all available data on physical comorbidities (ICD-10 diagnoses). Based on these data, we calculated the Charlson Comorbidity Index (CCI), the most widely used clinical index for the evaluation of comorbidities. The CCI weighs twenty chronic conditions as predictors of 1-year relative risk of death, and scores between 1 to 20 (Charlson, Pompei, Ales, & MacKenzie, 1987). Additionally, it was recorded whether an AD was prescribed at study entry or during the study period. We were also able to flag out several sub-populations with distinct type of malignancies: breast, lung, colon, prostate, and melanoma.

Analysis

Statistical analysis was conducted using SPSS version 22 (IBM Corporation, Armonk, New York). We performed descriptive statistics of socio-demographics, co-morbidities, and adherence levels across the total study population as well as across four adherence level groups (<20%, 20%-50%, 50%-80% and >80%). We used univariate associations (logistic regression and Kaplan Meier log rank) to assess the association between socio-demographics and clinical covariates and those who died or stayed alive during the study period. We used the multivariable Cox proportional hazard regression model to assess the adjusted association between risk of death and adherence level of AD medication controlling for confounders that were found to be significant in the univariate analysis [age (as a stratified variable), gender, physical co-morbidities modeled as CCI, smoking status and socio-economic status]. We tested the assumptions of the proportional hazard model using log (-log) plots. Although the database was lacking indication for AD prescription, we performed a sensitivity analysis, using the above methodology on a subpopulation within the cohort with a diagnosis of Major Depressive disorder (ICD10 codes: F.32-F.33). Finally, another sensitivity analysis was performed to test patients who were prescribed AD only during study period ("new users") compared to those who prior to their cancer diagnosis were being treated with AD for pre-existing depression. Hazard ratios (HR) and their 95% confidence interval (CI) are reported. Significance was considered when $p<0.001$, due to the extremely high-powered study. All analyses were two-tailed.

RESULTS

Population Characteristics

Population characteristics and mortality rates are shown in Table 1. Across the 42,075 people with cancer, the majority were women (64.7%) and 97% were above 40 years old. Most of the sample was native Israeli (88.5%). Unadjusted Mortality rates were higher for men than women (25.5% vs. 16.2%, respectively, $p<0.0001$) and those with higher CCI scores were more likely to die during the study period (28.8% on CCI >5 vs. 15.4% and 16.7% on CCI 3-4 and 0-2, respectively, $p<0.0001$ for all comparisons). Total number of person years at risk followed-up was 1,051,489. Mean follow up time was 25±15.9 months (range 1–47 months, median 25 months). Mean follow-up time of survivors was 27.5±15.8 months and mean time to death among those who died was 14.6±11.7 months.

Adherence

Thirty seven percent of the study sample discontinued AD within a month after the first prescription (i.e. they claimed only a single prescription) and 68.8% of the study sample discontinued the drug after less than 6 months. Adherence distribution and variables across adherence levels are shown in Table 2. The U-shaped adherence distribution indicated that 28.9% of AD users were non-adherent (n=12,092), 16.2% had poor adherence (n=6,763), 17.6% had moderate adherence (n=7,368) and 37.4% had good adherence (n=15,852).

Univariate Analysis

Unadjusted analyses (Table 2) show that those with non-adherence had the lowest mortality rate (16.3%) compared to the mortality rate of those with poor adherence (19.1%), moderate adherence (19.8%) or good adherence (21.9%; $p<0.001$ for all). These statistically significant differences were corroborated by a univariate Kaplan-Meier model (Log-rank Mantel-Cox $X^2=17.5$, $p=0.001$). Older age adults (>65 years) were more likely to have good adherence than being non-adherent (40.8% vs. 25.6% respectively, $p<0.001$, see Table 2). Furthermore, there were more severely physically-ill patients (CCI>5) in the good adherence group compared to the non-adherence group (40.3% vs. 27% respectively, $p<0.001$).

Multivariable analysis

The Cox proportional hazards model included mortality as the main outcome and variables significantly associated with mortality in the univariate analyses as covariates. Adjusted associations between adherence to the aggregate measure of AD and mortality appear in Figure 1. We analyzed association between adherence level and mortality using Cox Hazard model, while adjusting for age, gender, smoking status, socioeconomic status and physical co-morbidities. In analysis of the full sample with malignant neoplasm, the lowest HR for mortality was 0.77 [95%Confidence interval (CI): 0.66-0.72] at the level of 50%-80% adherence, compared to adherence below 20%. All levels of adherence above 20% were associated with significantly reduced HR for mortality (20%-50% adherence with HR 0.89 [95%CI: 0.83–0.95] and >80% adherence with HR 0.8 [95%CI: 0.76–0.85]).

The adjusted HR for mortality among men was 1.48 [95%CI: 1.42–1.55] compared to women. Other significant predictors of mortality were age (40-64: HR 0.21 [95%CI: 0.2-0.23], 65-74: HR 0.31 [95%CI: 0.29-0.34] and 75-84 HR 0.51 [95%CI: 0.48-0.54] relative to age 85+, $p<0.001$ for all), current or past smoking status (HR 1.1, [95%CI: 1.04-1.15], $p<0.0001$), low socioeconomic status (HR 1.1, [95%CI: 1.03-1.17], $p<0.0001$) compared to high socioeconomic status, and physical chronic comorbidity measured by CCI, with HR 0.59, [95%CI: 0.56-0.62], $p<0.0001$ for the 0-2 scores and HR 0.78, [95%CI: 0.74-0.82], $p<0.0001$ for the 3-4 scores compared to scores >5.

Cancer subtype analyses

Further examining the same association analysis within sub-populations of distinct types of malignancies (figure 1), we found similar pattern on most cancers but melanoma. Among the breast cancer sample (n=10,407), above 80% AD adherence was associated with HR 0.81 [95%CI: 0.71–0.94] reduced mortality compared to the least adherent below 20%. Among the colon cancer sample (n=5,091) the highest adherence level of 80% had a reduced risk of premature mortality versus the least adherent HR 0.82 [95%CI: 0.71–0.95]. Among the lung cancer sample (n=1,183) the highest adherence level of 80% had a reduced risk of premature mortality versus the least adherent 0.79 [95%CI: 0.64–0.98]. Among the prostate cancer subpopulation (n=2,960) the 80% adherence level had a reduced risk of premature mortality versus the least adherent 0.69 [95%CI: 0.56–0.84]. In contrast, no relationship was observed between the highest adherent melanoma sample (n=2,056) versus the least adherent (HR 0.9 [95%CI: 0.67–1.23, non-significant]).

Sensitivity Analyses

Analysis of sub-population with depression

We further performed a complementary analysis of a sub-population within the cohort that had a diagnosis of major depressive disorder (ICD10 codes: F.32-F.33), malignancy and were AD users (n=14,349). Across the whole group, during the follow-up period 2,938 (18.1%) patients died. Using the same survival model described above, similar results were found: HRs for mortality were 0.79 [95% CI: 0.69-0.9], 0.71 [95% CI: 0.64-0.8] and 0.68 [95% CI: 0.62-0.75] for poor, moderate and good adherence levels, respectively, in comparison to the non-adherence group. Variations in mortality were noted and there was consistent reduced mortality across all adherence groups for lung, prostate and breast cancer (see table 3). However, there was no evidence of an association between AD adherence and melanoma and colon cancer.

Analysis of "new users for AD"

About a third of the population entered the study with prescribed AD ("old users") and 67.5% (n=37,327) were prescribed AD for the first time during the study period, that is, a post cancer diagnosis ("new users"). Performing the same Hazard survival model for "new users" as a covariate revealed the same findings. HRs for mortality were 0.89 [95% CI: 0.83-0.96], 0.78 [95% CI: 0.73-0.84] and 0.72 [95% CI: 0.77-0.87] for poor, moderate and good adherence levels, respectively, in comparison to the non-adherence group.

DISCUSSION

The novel finding of our large population-based cohort study of patients with cancer treated by AD (N=42075) is that greater adherence to AD was associated with decreased risk of all-cause mortality during the 4-year follow-up period after adjusting for the relevant confounding risk factors for mortality including age, gender, socio-economic status, smoking status and physical comorbidities. We observed a similar relationship when we stratified the results according to the type of cancer including breast, colon, lung and prostate cancers, but not for melanoma patients. Interestingly, when we restricted our analysis to those with MDD and any type of cancer, there was evidence of reduced mortality in all AD groups. However, subgrouping for cancer type in those with MDD revealed that mortality was constantly reduced in all AD groups for lung, prostate and breast cancer, but not in any of the melanoma and colon cancer groups with MDD.

In the presence of the few and inconsistent reports of the relationship between AD use and premature mortality (Chubak et al., 2008; Stockler et al., 2007; Walker et al., 2012; Wernli et al., 2011), our finding utilizing a larger sample than all previous studies combined is important. In addition, our calculation of patient adherence may more accurately reflect the actual consumption of AD along the period they are prescribed, compared to previous studies which only considered if AD were used as a binary variable (Bambauer et al., 2006; Sawada et al., 2009; World Health Organization, 2003).

Our findings contradict the pharmacoepidemiological report in a sample of 3,058 breast cancer patients (Wernli et al., 2011), suggesting AD use may be associated with 1.5-fold increased all-cause mortality. However, that study was based on patients' reports

via mail and was therefore subject to substantial recall and selection biases. In addition, it is limited by examining AD use and not adherence. Our data is in partial agreement with the report of 17,883 colorectal cancer or glioma patients(Walker et al., 2012) which observed no effect of TCA use on patient mortality, as when we restricted our sample to only those with MDD and colon cancer we found no evidence of the impact of AD adherence on mortality. However, that study was limited by substantial missing data with respect to major confounding factors such as smoking and obesity. Moreover, focusing only on TCA, representing a small portion of AD, is not generalizable to more commonly prescribed medications. Finally, no effect of AD on mortality was also reported in a sample of 1,306 women with breast cancer (Chubak et al., 2008). However, the authors were concerned by some key unmeasured variables, including potentially misclassified data. Furthermore, similarly to all previous reports, the evaluation of AD use as a binary variable is a major limitation.

Our findings not only indicate that adherence to AD is associated with increased survival in patients with cancer, but that this relationship may be to some extent continuous, that is, even partial adherence to AD may be beneficial in terms of survival. However, the better survival of the low adherence group vs. none adherence, and the moderate adherence group vs. the low adherence did not repeat itself when comparing the high adherence vs. moderate adherence groups, indicating a possible ceiling effect of the benefit of AD adherence in terms of ameliorating survival. In addition, we observed some suggestion of cancer type specific variations in terms of mortality risk in those with MDD.

Surprisingly, the relationship between AD adherence and survival in the cohort, that was similarly observed in the breast, colon, prostate and lung cancer patients, did not repeat in the melanoma subgroup. Only scarce mixed pre-clinical data are available regarding a possible effect of AD on melanoma tumors. Whereas some studies suggested that certain ADs may be effective in inhibiting tumor growth in a murine model, have an in-vitro cytotoxic activity against human melanoma cells or possess antioxidant activity in mice, other studies indicated that SSRIs may increase mice brain metastases or not affect them (Boia-Ferreira et al., 2017; Herr, Mohile, van, Brown, & Rich, 2016). To the best of our knowledge, no clinical studies evaluated this question, which is particularly intriguing since melanocyes originate from the embryonic ectoderm, similarly to the central nervous system.

Similarly to our previous reports on mortality in other AD-using populations (Krivoy et al., 2015; Krivoy et al., 2016; Krivoy et al., 2017; Shoval et al., 2017), our unadjusted analyses in the present study showed increased rate of death in the higher adherence levels. As previously discussed broadly in these publications, we attribute this finding mainly to a more drug adherent behavior in the older and highly co-morbid patients, therefore such findings demonstrates the importance of having the capability to adjust for importance confounders.

Whilst our data addresses an important gap within the literature, the findings should be interpreted in light of its limitations. The primary analyses did not include data regarding the indication as mental health diagnosis data in the database was incomplete. Additionally, data on causes of death was also not available, and thus we were unable to discriminate between death due to cancer, suicide and other causes. However, we

considered all-cause mortality a preferable outcome measure to evaluate the long-term global impact of AD adherence on cancer patients' survival. Finally, though we used a reliable indicator for co-morbid physical conditions of the patients, there might be still residual confounding by unmeasured variables, such as grading and staging of the neoplasm.

In conclusion, the present four-year follow-up study is the first to demonstrate the inverse association between adherence to AD and all-cause mortality in a general population-based large cohort of patients with cancer. This relationship is systematically repeated in all subtypes of cancer we studied, except for melanoma. Similarly to our previous studies in the general population and in certain other major physical disorders (Krivoy et al., 2015; Krivoy et al., 2016; Krivoy et al., 2017; Shoval et al., 2017), the beneficial effect of adherence to AD may be at least equally important in the high-risk population of patients with cancer. Psychiatrists, Oncologists and primary-care physicians should step up their efforts to sustain and enhance their patients' adherence to AD, as it may be associated with increased life-expectancy.

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Table 1: Total patient population with cancer (N=42075) characteristics and mortality rates across demographic and clinical covariates.

		Population		Mortality	
		n	%	n	%
Total		**42075**		**8194**	**19**
Males		14864	35.3	3791	25.5
Females		27211	64.7	4403	16.2
Age at study entry	0-17	71	0.2	7	9.9
	18-24	121	0.3	4	3.3
	25-39	1065	2.5	73	6.9
	40-64	13005	30.9	1354	10.4
	65-74	10099	24.0	1563	15.5
	75-84	13089	31.1	3240	24.8
	>85	4625	11.0	1953	42.2
Native		37230	88.5	7290	19.6
Immigrant		4845	11.5	904	18.7
Socio-economic status	Low	13402	31.9	2333	17.4
	Moderate	17836	42.4	3649	20.5
	High	12701	30.2	2196	17.3
CCI	0-2	13858	32.9	2316	16.7
	3-4	16774	39.9	2588	15.4
	>5	11418	27.1	3285	28.8
Smoking status	Never	29374	69.8	5613	19.1
	Past or Current	12220	29.0	2381	19.5
Breast cancer		10407		1333	10
Colon cancer		5091		1140	17
Lung cancer		1183		561	31.1
Prostate cancer		2960		608	15.4
Melanoma		2056		287	10.7

CCI – Charlson's Comorbidity Index

Table 2: Population characteristics across adherence levels (N=42075). Percentage represents proportions of variable across levels of adherence (row).

		None <20%		**Poor** 20%-50%		**Moderate** 50%-80%		**Good** >80%		**Total**
		n	**%**	**n**	**%**	**N**	**%**	**n**	**%**	
Gender	Male	4289	29	2403	16	2608	18	5564	37	14864
	Female	7803	29	4360	16	4760	17	10288	38	27211
Age at study entry	0-17	17	24	15	21	16	23	23	32	71
	18-24	37	31	20	17	22	18	42	35	121
	25-39	387	36	203	19	176	17	299	28	1065
	40-64	4508	35	2183	17	2186	17	4128	32	13005
	65-74	2912	29	1648	16	1765	17	3774	37	10099
	75-84	3227	25	2008	15	2323	18	5531	42	13089
	85+	1004	22	686	15	880	19	2055	44	4625
Socio-economic status	Low	4068	30	3679	27	1993	15	3662	27	13402
	Mod.	5319	30	2016	11	3269	18	7232	41	17836
	High	2680	21	3026	24	2077	16	4918	39	12701
Smoking	Never	8472	29	4717	16	5099	17	11086	38	29374
	Ever	3499	29	1968	16	2190	18	4563	37	12220
Immigrant	No	10499	28	5874	16	6517	18	14340	39	37230
	Yes	1593	33	889	18	851	18	1512	31	4845
CCI*	0-2	3997	29	2271	16	2521	18	5069	37	13858
	3-4	5004	30	2683	16	2911	17	6176	37	16774
	>5	3078	27	1806	16	1933	17	4601	40	11418
Mortality**		1970	16	1292	19	1458	20	3474	22	8194
Total		12092		6763		7368		15852		42075

* CCI – Charlson's Comorbidity Index

** Mortality rate within adherence group

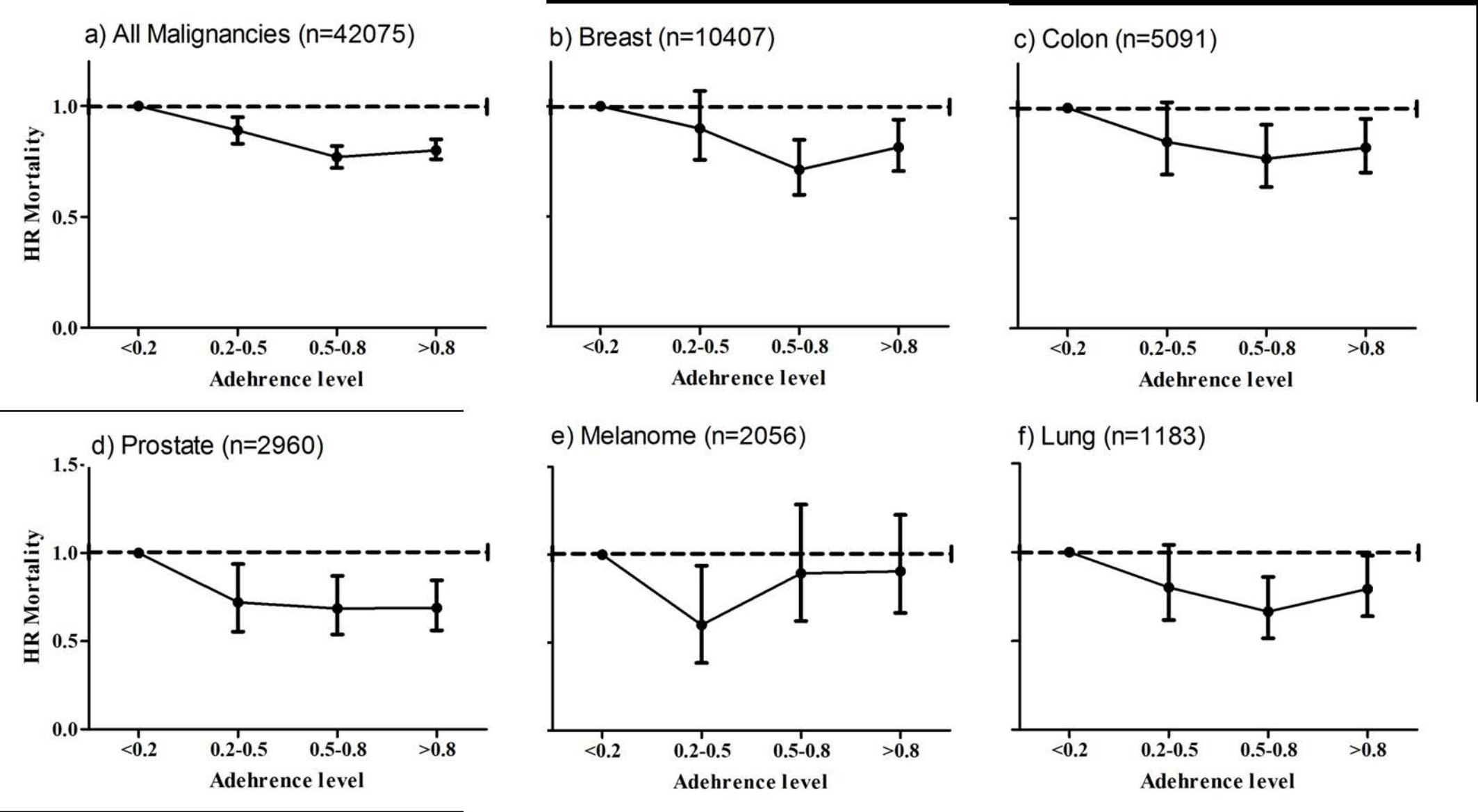
Table 3: Multivariate survival analysis of the effect of antidepressants' adherence in sub-population with diagnoses of depression and malignancy, by type of malignancy. Model is adjusted for age, sex, smoking status, socioeconomic status and Charslon's comorbidity index. Reference group is non-adherence (<20%).

Cancer type	N	n died	Crude mortality (%)	HR >80% adherence	HR 50%-80% adherence	HR 20%-50% adherence
Melanoma	620	92	13.3	1.23 [0.63-2.37]	1.3 [0.62-2.75]	0.58 [0.21-1.57]
Lung	367	161	36.3	**0.52 [0.34-0.79]**	**0.56 [0.35-0.89]**	**0.45 [0.26-0.77]**
Prostate	915	223	21.4	**0.44 [0.31-0.62]**	**0.4 [0.27-0.61]**	**0.5 [0.32-0.8]**
Colon	1746	402	20.1	0.8 [0.62-1.06]	0.73 [0.52-1.01]	0.89 [0.62-1.27]
Breast	3574	497	12.5	**0.66 [0.52-0.85]**	**0.69 [0.52-0.92]**	**0.69 [0.5-0.95]**

HR- Hazard ratio for mortality

Figure legend

Figure 1: Relative hazard ratios (HR) for mortality by adherence level during 4 years follow-up (a, all malignancies, n=42075). Non-adherence level (<20%) serves as the reference. The model is based on Cox multivariate survival model adjusted for gender, age, smoking, socio-economic status and Charlson's comorbidity index. Each box (b-f) represents subpopulation with specific cancer type.


a) All Malignancies (n=42075)
b) Breast (n=10407)
c) Colon (n=5091)
d) Prostate (n=2960)
e) Melanome (n=2056)
f) Lung (n=1183)
HR Mortality
1.5
1.0
0.5
0.0
<0.2
0.2-0.5
0.5-0.8
>0.8
Adehrence level